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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,223	01/27/2006	Jaya Sivaswami Tyagi	4544-060174	3494
	7590 09/04/200 AW FIRM, P.C.	EXAMINER		
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436 SEVENTH AVENUE PITTSBURGH, PA 15219			ART UNIT	PAPER NUMBER
			1637	
			MAIL DATE	DELIVERY MODE
			09/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary		Application No.	Applicant(s)				
		10/566,223	TYAGI ET AL.				
		Examiner	Art Unit				
		ANGELA BERTAGNA	1637				
 Period for	The MAILING DATE of this communication app Reply	ears on the cover sheet with the c	orrespondence address				
A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.  - Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).							
Status							
1)⊠ F	Responsive to communication(s) filed on <u>27 Ma</u>	av 2008					
/—		action is non-final.					
<i>,</i> —	Since this application is in condition for allowance except for formal matters, prosecution as to the merits is						
•	closed in accordance with the practice under <i>Ex parte Quayle</i> , 1935 C.D. 11, 453 O.G. 213.						
Dispositio	n of Claims						
4) X  C	Claim(s) <u>117-120 and 124-132</u> is/are pending i	n the application.					
•	4a) Of the above claim(s) 130-132 is/are withdrawn from consideration.						
	_ '						
	6)⊠ Claim(s) <u>117-120 and 124-129</u> is/are rejected.						
	Claim(s) 117 and 118 is/are objected to.						
	Claim(s) are subject to restriction and/or	election requirement.					
Application Papers							
	ne specification is objected to by the Examine						
	ne drawing(s) filed on is/are: a) ☐ acce						
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).							
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).							
11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.							
Priority un	der 35 U.S.C. § 119						
<ul> <li>12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).</li> <li>a) All b) Some * c) None of:</li> <li>1. Certified copies of the priority documents have been received.</li> <li>2. Certified copies of the priority documents have been received in Application No</li> <li>3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).</li> <li>* See the attached detailed Office action for a list of the certified copies not received.</li> </ul>							
Attachment(s	s) of References Cited (PTO-892)	4) 🔲 Interview Summary	(PTO-413)				
2) Notice of Draftsperson's Patent Drawing Review (PTO-948) Paper No(s)/Mail Date							
	ation Disclosure Statement(s) (PTO/SB/08) No(s)/Mail Date	5) Notice of Informal P 6) Other:	акент Аррисация				

### **DETAILED ACTION**

# Status of the Application

1. Applicant's response filed on May 27, 2008 is acknowledged. Claims 117-120 and 124-132 are currently pending. In the response, Applicant amended claims 117 and 124 and cancelled claims 121-123. Claims 130-132 are withdrawn from consideration as being drawn to a non-elected invention.

The following objections and rejections are withdrawn in view of Applicant's amendment: (1) the objection to the abstract, (2) the objection to the specification, and (3) the rejection of claims 117-129 under 35 U.S.C. 112, second paragraph.

Applicant's arguments regarding the rejections made under 35 U.S.C. 103(a) have been fully considered, but they were not found persuasive for the reasons set forth in the "Response to Arguments" section.

The following are new grounds of rejection necessitated by Applicant's amendments to the claims. Accordingly, this Office Action is made FINAL.

## Election/Restrictions

2. This application contains claims 130-132 drawn to an invention nonelected with traverse in the reply filed on September 18, 2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the

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currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

## Claim Objections

3. Claims 117 and 118 are objected to because of the following informalities: These claims contain typographical and/or grammatical errors.

In claim 117, the following changes are suggested:

- (a) addition of the word "and" after the word "sensitive",
- (b) deleting the parentheses enclosing the phrase "comprising guanidinium hydrochloride (GuHCl)",
  - (c) replacing the word "to" with the word "with" in step (b),
  - (d) adding the word "a" before the word "pellet" in step (d), and
  - (e) adding the word "a" before the words "processed sample" in step (g).

In claim 118, replacing "homogenizing for time duration" with "homogenizing for a time duration of" is suggested.

Appropriate correction is required.

## Claim Rejections - 35 USC § 103

- 4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:
  - (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

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having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 117-120 and 124-126 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chakravorty et al. (FEMS Microbiology Letters (2001) 205: 113-117; cited previously) in view of Jaber et al. (Tubercle and Lung Disease (1995) 76: 578-581; cited previously).

These claims are drawn to a method for processing clinical samples for analysis by smear, culture, or PCR methods using a composition comprising three solutions.

Regarding claim 117, Chakravorty teaches a method comprising:

- (a) obtaining a clinical sample (page 114, section 2.1)
- (b) mixing 1.5 2 volumes of a first solution with the sample and homogenizing the sample (see page 114, section 2.2.1, where solution 1 of Chakravorty comprises: 5 M GITC, 50 mM Tris-Cl, pH 7.5, 25 mM EDTA, 0.5% Sarcosyl, and 0.2 M β-mercaptoethanol)
- (c) adding a second solution to the homogenate (solution 1 inherently includes water) and centrifuging to obtain a pellet (section 2.2.1 on page 114)
  - (d) washing the pellet with the first solution (page 114, section 2.2.2)

- (e) washing the pellet of step (d) with water (page 114, section 2.2.2)
- (f) resuspending the water-washed pellet in solution A (10% Chelex-100), solution B (Triton X-100 at 0.3%), and solution C (Tween 20 at 0.3%) (page 114, section 2.2.3).

Chakravorty further teaches that the resulting solution is used for PCR amplification of mycobacterial DNA (page 114).

Regarding claim 118, Chakravorty teaches homogenization for 30-60 seconds (page 114, column 1).

Regarding claim 119, Chakravorty teaches that the above process can be performed in approximately three hours (page 116, column 2).

Regarding claim 120, the 5 M concentration of GITC is about 4 M, about 5 M, and about 6 M, and the 0.2 M concentration of  $\beta$ -mercaptoethanol is about 0.1 M or about 0.2 M. This concentration of  $\beta$ -mercaptoethanol is also within the claimed range of 0.1-0.2 M. It is further noted that the intended use recitations "for processing samples for culture and smear", "for processing of samples for culture, smear, and PCR", and "samples processed for smear and PCR" have not been accorded patentable weight since they are intended use recitations (see MPEP 2111.02 II).

Regarding claim 124, Chakravorty teaches obtaining PCR-amplifiable DNA by adding 0.03% Triton X-100, which is within the claimed range of 0.01 - 0.1% (page 115, column 1). RNA is also inherently purified in the method of Chakravorty.

Regarding claim 125, the method of Chakravorty is performed at pH 7.5 (page 114).

Regarding claim 126, the samples used by Chakravorty were inherently stored at about - 20°C for a time up to two months. It is also inherent that the samples can be processed for PCR, smear microscopy, and culture.

Chakravorty teaches the use of 5 M GITC in the first solution rather than 4-6 M GuHCl required by claim 117. Also, Chakravorty teaches that the above sample processing method can be performed in approximately three hours (page 116, column 2) rather than the 1-2 hours required by claim 119. Regarding claim 124, Chakravorty teaches lysis in the presence of 0.03% Triton X-100, but does not teach that this embodiment of the method is performed in the absence of Solutions A, B, and C. Finally, regarding claim 125, Chakravorty teaches performing the method at a slightly alkaline pH of 7.5 rather than at neutral pH.

Jaber teaches a method for isolating DNA from *Mycobacterium tuberculosis* (pages 578-579). The method of Jaber comprises the following steps: (1) cell lysis in 6 M GuHCl, 50 mM EDTA, 1 mM 2-mercaptoethanol, 0.05% Tween 80; (2) ethanol precipitation, (3) washing with lysis buffer, (4) phenol-chloroform and chloroform-isoamyl alcohol extraction, and (5) ethanol precipitation (see page 579).

Regarding claim 117, Jaber teaches that the chaotropic agent guanidinium hydrochloride, (GuHCl), "inactivates DNase and RNase, dissociates nucleoprotein, and disturbs cellular and subcellular structure, and its pH and ionic strength favor the native form of DNA (page 579, column 2)."

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to substitute GuHCl for GITC in the sample processing method taught by Chakravorty.

An ordinary artisan would have been motivated to do so, because as evidenced by the teachings

of Jaber (page 579-580), GuHCl and GITC are art-recognized equivalents useful for the same purpose. As noted in MPEP 2144.06, substitution of art-recognized equivalents useful for the same purpose is *prima facie* obvious in the absence of unexpected results. Furthermore, an ordinary artisan would have recognized that unlike GITC, GuHCl is nontoxic, and therefore, would have been motivated to use this non-toxic equivalent in order to minimize the use of hazardous chemicals in the method of Chakravorty. An ordinary artisan also would have been motivated to perform the method of Chakravorty using Triton X-100 in the absence of solutions A, B, and C, because Chakravorty taught that this detergent resulted in the best lysis and inhibitor removal (page 115) and that the Chelex-100 adsorption step (i.e. solution A treatment) only served to remove residual inhibitors that would not be present in samples with a low level of contaminants (page 116). An ordinary artisan would have been motivated to eliminate unnecessary processing steps, such as treatment with solutions A, B, and C, because Chakravorty taught that multi-step processes resulted in sample loss and presented more contamination opportunities (page 116). Finally, regarding claims 118, 119, and 125, an ordinary artisan would have been motivated to optimize the homogenization time, the total processing time, and the pH at which the method was conducted in order to achieve the desired results. For example, an ordinary artisan would have been motivated to optimize the homogenization time in order to obtain maximal lysis without damaging the DNA. An ordinary artisan also would have been motivated to minimize the time required for performance of the method in order to increase efficiency. Moreover, as noted in MPEP 2144.05, "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)."

Routine optimization is not inventive and no evidence has been presented to suggest that the selection of the claimed homogenization times, processing times, or pH values was other than routine or that the results should be considered to be unexpected compared to the prior art. Thus, the methods of claims 117-120 and 124-126 are *prima facie* obvious over Chakravorty in view of Jaber in the absence of secondary considerations.

6. Claims 127-129 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chakravorty et al. (FEMS Microbiology Letters (2001) 205: 113-117; cited previously) in view of Jaber et al. (Tubercle and Lung Disease (1995) 76: 578-581; cited previously) and further in view of GenBank Accession No. U22037 (March 1999; cited previously) and further in view of Marchetti et al. (Journal of Clinical Microbiology (1998) 36(6): 1512-1517; cited previously) and further in view of Buck et al. BioTechniques (1999) 27(3): 528-536; cited previously).

The combined teachings of Chakravorty and Jaber result in the method of claims 117-120 and 124-126, as discussed above.

Regarding claims 127-129, Chakravorty teaches using a set of primers designed from the *Mycobacterium tuberculosis* devR gene to amplify DNA isolated using the above method (page 114, column 2). However, Chakravorty does not teach amplification using two sets of primers, wherein each primer set targets the devR gene and produces amplification products of 308 bp and 164 bp.

GenBank Accession No. U22037 teaches the complete nucleotide sequence of the *Mycobacterium tuberculosis* devR gene. The primers taught by Chakravorty are contained in this sequence and produce a 513 bp amplification product.

Marchetti teaches methods for amplifying *Mycobacterium tuberculosis* DNA by PCR (see abstract and page 1513). Marchetti compared the sensitivity of four different PCR primer pairs and determined that the use of primers designed to amplify shorter targets resulted in more sensitive detection than primers designed to amplify longer targets (see abstract and pages 1514-1515). Marchetti further stated, "PCR3 and PCR4, whose final amplification products are 106 and 123 bp long, respectively, showed the best results in terms of sensitivity compared to those of PCR1 and PCR2, which amplify longer fragments (223 and 143 bp, respectively). This suggests the need to choose the correct primers, with those amplifying relatively shorter DNA sequences, which are thus less prone to fragmentation, being favored (page 1515, column 2)."

Buck analyzed the effect of primer design strategy on the performance of DNA sequencing primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95

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control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that the selection and use of primers in primer extension methods yields predictable results.

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It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to utilize any set of primer pairs designed from the known Mycobacterium tuberculosis devR gene to amplify DNA isolated by the method resulting from the combined teachings of Chakravorty and Jaber. Since Marchetti taught that the use of primers designed to amplify short targets in the Mycobacterium tuberculosis genome resulted in increased sensitivity (pages 1514-1515), an ordinary artisan would have been motivated to design primer pairs targeting sequences shorter than the 513 bp region targeted by Chakravorty. An ordinary artisan would have had a reasonable expectation of success designing these primers since the complete devR gene sequence was known in the art at the time of invention as evidenced by GenBank Accession No. U22037. An ordinary artisan also would have had a reasonable expectation of success in using the primers in the method resulting from the combined teachings of Chakravorty and Jaber, since Buck demonstrated that essentially all primers were capable of an equivalent degree of extension when hybridized to a complementary target. Therefore, absent any secondary considerations, the claimed methods are *prima facie* obvious in view of the combined teachings of Chakravorty, Jaber, Marchetti, GenBank Accession No. U22037, and Buck.

Attention is also directed to *KSR Int'l Co. v. Teleflex Inc.* (550 U.S.\_\_\_\_\_, 127 S. Ct. 1727 (2007)) where the Supreme Court determined that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that

instance the fact that a combination was obvious to try might show that it was obvious under § 103 (KSR, 550 U.S. at , 82 USPQ2d at 1397)."

In the instant case, as discussed above, an ordinary artisan would have been motivated to apply the teachings of Marchetti regarding dependence of PCR sensitivity on target length to the method resulting from the combined teachings of Chakravorty and Jaber. The complete nucleotide sequence of the Mycobacterium tuberculosis gene disclosed in GenBank Accession No. U22037 presented the ordinary artisan with a finite number of possible primers for amplification. Then, since Buck taught that a large number of primers designed to detect the same target functioned reasonably well (see above), an ordinary artisan would have expected predictable results, and thus would have had a reasonable expectation of success, when testing the finite number of possible amplification primers suggested by applying the teachings of Marchetti to the devR gene targeted by Chakravorty. Therefore, the methods of claims 127-129 are *prima facie* obvious over the cited references in the absence of secondary considerations.

### Response to Arguments

7. Applicant's arguments filed on May 27, 2008 have been fully considered, but they were not persuasive.

Regarding the rejection of claims 117-126 under 35 U.S.C. 103(a) as being unpatentable over Chakravorty in view of Jaber, Applicant argues that the references cannot be combined, because Jaber does not teach that guanidinium hydrochloride (GuHCl) can be substituted for guanidinium isothiocyanate (GITC) (see page 9). In view of the cancellation of claims 121-123, this rejection currently applies to claims 117-120 and 124-126. Applicant's argument was not

persuasive, because the teachings of Jaber that GuHCl was a chaotropic agent useful for cell lysis, inactivation of nucleases, dissociation of nucleoproteins, and disturbance of cellular and subcellular structures (see page 579) would have indicated to the ordinary artisan that GuHCl and GITC were equivalent chaotropic agents known to be useful for the same purpose, namely cell lysis and protein denaturation and/or inactivation. Therefore, an ordinary artisan would have been motivated to substitute GuHCl for GITC when practicing the method of Chakravorty with a reasonable expectation of success. Also, as noted in MPEP 2144.07, it is *prima facie* obvious to select a known material based on its suitability for the intended purpose. Since GuHCl was known in the art to be useful for achieving cell lysis, protein denaturation and/or inactivation, and dissociation of nucleoprotein complexes, as evidenced by the teachings of Jaber (see page 579), an ordinary artisan would have been motivated to utilize GuHCl in the method of Chakravorty with a reasonable expectation of success. Since Applicant's arguments were not found persuasive, the rejection has been maintained.

Regarding the rejection of claims 127-129 under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Chakravorty, Jaber, GenBank Accession No. U22037, Marchetti, and Buck, Applicant argues that there is no motivation to select the claimed primers from the large number of primers suggested by the prior art (see page 9). This argument was not persuasive, because as discussed previously, an ordinary artisan would have been motivated to apply the teachings of Marchetti regarding dependence of PCR sensitivity on target length to the method resulting from the combined teachings of Chakravorty and Jaber. Application of the teachings of Marchetti to the method resulting from the combined teachings of Chakravorty and

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Jaber would result in the design of primer pairs (*e.g.* the claimed primer pairs) that produce shorter amplified products.

Also, in the recent decision *KSR Int'l Co. v. Teleflex Inc.* (550 U.S.\_\_\_\_\_, 127 S. Ct. 1727 (2007)), the Supreme Court determined that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103 (*KSR*, 550 U.S. at , 82 USPQ2d at 1397).

In this case, the complete nucleotide sequence of the *Mycobacterium tuberculosis* gene was disclosed in the prior art of GenBank Accession No. U22037 and presented the ordinary artisan with a finite number of possible primers for amplification. Since Buck taught that a large number of primers designed to detect the same target functioned reasonably well (see above), an ordinary artisan would have expected predictable results, and thus would have had a reasonable expectation of success, when testing the finite number of possible amplification primers suggested by applying the teachings of Marchetti to the devR gene targeted by Chakravorty. The KSR decision makes clear that an explicit teaching, suggestion, or motivation is not required for a *prima facie* case of obviousness when an ordinary artisan would have combined known elements according to known procedures with predictable results (see MPEP 2141). In this case, the complete nucleic acid sequence of the devR gene was known in the art as evidenced by GenBank Accession Number U22037. Also, methods of primer synthesis and design were known in the art and were predictable as evidenced by the teachings of Chakravorty, Buck, and Marchetti. Thus, an ordinary artisan would have designed the claimed primers using the known

devR sequence and known oligonucleotide synthesis methods and would have expected predictable results in doing so. Thus, in the absence of secondary considerations, the claimed primers are *prima facie* obvious over the cited references. Since Applicant's arguments were not found persuasive, the rejection has been maintained.

#### Conclusion

8. No claims are currently allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/GARY BENZION/ Supervisory Patent Examiner, Art Unit 1637